REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 1-15, 18-41, 57-49 are in the application.

I. OBVIOUSNESS-TYPE DOUBLE PATENTING

Claims 1-15, 21, 23, 31-32, 37-41 and 47 stand provisionally rejected on obviousness-type double patenting grounds as allegedly unpatentable over claims 48-59 of copending Application Serial No. 09/763,955. Applicants will consider filing a Terminal Disclaimer when otherwise allowable subject matter is indicated.

II. THE 35 U.S.C. §112, FIRST PARAGRAPH, REJECTIONS

Claims 1-15, 18-32 and 47-49 stand rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for the treatment of congenital mitochondrial disease, Alzheimer's Disease, Huntington's Disease, neuromuscular degenerative disease, and pathophysiological consequences of mitochondrial respiratory chain dysfunction, allegedly does not reasonably provide enablement for the prevention of congenital mitochondrial disease, Alzheimer's Disease, Huntington's Disease, neuromuscular degenerative disease, and pathophysiological consequences of mitochondrial respiratory chain dysfunction. This rejection is respectfully traversed.

The Action acknowledges the arguments presented on June 30, 2005 but views them as not persuasive, despite the submission of references in support of Applicants' position. The Action states that the references submitted by Applicants have not been

considered as they were not properly cited by way of an Information Disclosure Statement.

In light of this position, attached is an Information Disclosure Statement together with a completed Form PTO./SB/08a listing the references discussed both in the section of the response dealing with lack of enablement and the section dealing with obviousness. The requisite IDS fee is also attached, along with the three month extension fee. Except for the last eight listed references (copies of which are enclosed), the Office has already received copies of the references listed on the attached PTO/SB/08a, and further copies of those references previously supplied are not enclosed herewith. Should the Office require additional copies of those references, it is requested that the undersigned be so advised. The Examiner is requested to initial the attached PTO/SB/08a and to return a copy of the initialed document to the undersigned with the next paper to issue in this case.

Saydoff *et al.* "Oral uridine pro-drug PN401 decreases neurodegeneration, behavioral impairment, weight loss and mortality in the 3-nitropropionic acid mitochondrial toxin model of Huntington's disease", *Brain Res.* (2003) 994(1):44-54 discusses the effects of triacetyluridine (PN401) on prevention of neuronal damage and its functional consequences in a model of Huntington's disease involving the mitochondrial respiratory chain toxin 3-nitropropionic acid (3-NP). The Abstract states that treatment with PN401 "almost completely prevented the neuronal damage due to 3NP and completely prevented mortality." The experimental work leading to this conclusion is reported in Experiments 1 and 2 described at page 50, left hand column.

These experimental results confirm the efficacy of the method for preventing Huntington's disease taught in the specification.

Gines *et al.*, "Specific progressive cAMP reduction implicates energy deficit in presymptomatic Huntington's disease knock-in mice", *Hum Mol Genet.* (2003);12(5):497-508 (Abstract) presents new data obtained in a mouse model of Huntington's disease. The Abstract indicates that defects in gene transcription and mitochondrial function are associated with Huntingdon's disease. It appears that Huntingdon's disease causes regions of the brain to undergo degeneration (as detected by silver staining). As presently advised, treatment with triacetyluridine reduces loss of cells, with the result that the disease is prevented from being as severe as it otherwise would be without such treatment.

The data included in the present application involve both "treatment" and "neuroprotective" effects of a pyrimidine nucleotide precursor(s), used as a therapeutic for disorders involving mitochondrial respiratory chain enzyme impairment. The experimental approach involved initiating treatment with the pyrimidine nucleotide precursor triacetyluridine prior to the administration of the mitochondrial toxin. The complex I respiratory chain inhibitor MPTP model of Parkinson's disease (PD) (Example 7), Complex II respiratory chain inhibitor 3-nitropropionic acid model of Huntington's disease (HD) (Example 9) and the Complex IV respiratory chain inhibitor azide model of Alzheimer's disease (AD) (Example 12) included pretreatment with triacetyluridine. The treatment with triacetyluridine continued throughout the course of these examples. The sum therapeutic effect of triacetyluridine in the PD and HD and stroke models was a combined neuroprotective/cytoprotective and treatment effect. In the Complex IV

respiratory chain inhibitor azide model of AD, there was a decrease in mortality due to pretreatment with triacetyluridine. If the mitochondrial impairment was not extremely severe (as was the case with the use of azide at only the 40 µg/hr dose), pretreatment/treatment with triacetyluridine was able to completely prevent mortality.

It is Applicants' position that the correct connotation of "preventing" as used in the presently claimed invention is prophylactic administration of compounds of the invention which prevents progression or full manifestation of diseases related to essentially irreversible mitochondrial defects. The specification is enabling with respect to such prevention in the context of the presently claimed invention for the above-discussed reasons. Just as few or no other classes of drugs used for treatment of chronic diseases prevent or reverse all symptoms completely, the standard for successful prevention in medical practice is prevention of symptoms of a disorder (especially a progressive or episodically exacerbating disorder) from being as bad as it would be without the drug. This is particularly significant for mitochondrial disorders which, as a class, often undergo exacerbations, either episodically or permanently.

The effect of an acylated ribonucleoside derivative(s) to "prevent" diseases involving mitochondrial dysfunction can be described as a "neuroprotective" and a "cytoprotective" effect (to include non-central nervous system cells). The term "neuroprotective" has been used to refer to the ability of a therapeutic method, if given prior to the initial initiation of factors that cause the disease ("pretreatment"), to reduce the severity or delay the onset and/or slow the progression of tissue damage and functional impairment (see: Ferrante, et al., 2000; Du, et al., 2001; Ravina, et al., 2003,

of record). The *in vivo* evidence described in the present case further supports the disease preventative effects achieved by the presently claimed method.

The Action notes that the references were published in 2003, later than the date of filing of the present application in 2001. However, the references are being relied upon to show how someone would have understood the term "prevention" as used in the context of the presently claimed invention as of 2001. The understanding of one of ordinary skill would not have changed significantly over the time period from the 1998 priority date of the present application to the date of the references in 2003.

The prevention aspect of the present invention (as well as the treatment aspect) is therefore supported by an enabling disclosure. Withdrawal of the outstanding 35 USC 112, first paragraph, rejections is accordingly respectfully requested.

III. THE OBVIOUSNESS REJECTION

Claims 1-15, 18-32 and 37-41 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Page et al., *Proc Natl. Acad. Sci. USA*, Vol. 94, 11601-1166 (1997) in combination with U.S. 6,316,426 to von Borstel et al. This rejection is respectfully traversed.

The Action asserts, on page 8 of the action, that "Developmental delay, seizures, ataxia, recurrent infections, severe language deficit, and an unusual behavioral phenotype characterized by hyperactivity, short attention span, and poor social interaction are 'pathophysiological consequences of mitochondrial respiratory chain dysfunction' ". This assertion is respectfully traversed. It is simply not true that all of the

conditions recited in the Action are necessarily 'pathophysiological consequences of mitochondrial respiratory chain dysfunction'.

As it is well recognized that unrelated diseases can have overlapping symptoms, it is equally well recognized that the effectiveness of a particular drug in treating a symptom in one disorder does not necessarily, or even generally, imply that the drug will be useful in treating other diseases with similar symptoms. For example, epilepsy or related seizure disorders may be caused by tumors, poisons, mitochondrial defects, or simply self-amplifying circuits of neural activity without other organic defects causing the seizures. Seizure episodes in a susceptible person can be triggered by progesterone deficits, e.g. associated with the menstrual cycle. Although the clinical symptoms – seizures – may look similar, the treatments will vary according to the underlying problem.

Valproate (Depakote) is a widely-used anti-seizure medication, but it can actually exacerbate seizures (and other manifestations of mitochondrial disease) caused by mitochondrial deficits, due to its inhibitory effect on mitochondrial respiration. For someone with seizures triggered by a progesterone deficit, progesterone or an analog thereof is more appropriate than increased doses of other anti-seizure medications, which have debilitating side effects at higher doses. Some seizure disorders associated with foci of hyperexcitable neurons are best treated with electrodes inserted into the brain, which would be inappropriate for seizures caused by metabolic deficits. As further evidence of this, attached are copies of the following papers which are briefly discussed below.

Lam et al (Eur J Pediatr. 1997 Jul;156(7):562-4. Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) triggered by valproate therapy. Lam CW, Lau CH, Williams JC, Chan YW, Wong LJ. Department of Pathology, Princess Margaret Hospital, Lai Chi Kok, Hong Kong) have reported that:

> "...valproate should not be given to patients suspected of having mitochondrial diseases. In addition, for patients whose seizures worsen with valproate therapy, an inborn error of mitochondrial metabolism should be suspected. The underlying mitochondrial DNA defects should be sought for family screening and genetic counselling."

Likewise, Krahenbuhl et al (Liver. 2000 Jul;20(4):346-8; Mitochondrial diseases represent a risk factor for valproate-induced fulminant liver failure. Krahenbuhl S, Brandner S, Kleinle S, Liechti S, Straumann D. Department of Clinical Pharmacology, University of Berne, Switzerland) have reported that "Mitochondrial diseases should therefore be considered as a risk factor for valproate-induced liver failure and be excluded before treatment with valproate."

Another example of a condition which can arise from different causes is arthritis. Pain in the joints can be caused by autoimmune attack (rheumatoid arthritis, psoriatic arthritis, or lupus-associated), osteoarthritis, infections, e.g. lime disease, gout, deposition of antibody complexes, etc. All of these disorders may present with joint pain as a predominant symptom, but the appropriate treatments are very different for each of these different diseases that underlie similar symptoms, e.g. anti-TNF therapies for rheumatoid arthritis, B-Cell suppressors for Lupus, nonsteroidal anti-inflammatory drugs for osteoarthritis, antibiotics for Lyme disease, allopurinol for gout. Attention in this regard is directed to Ritchie et al., "Diagnostic Approach to Polyarticular Joint Pain", *American Family Physician*, 68, 6, 1151-1160 (2003), which states (in the Abstract) that

"Identifying the cause of polyarticular joint pain can be difficult because of the extensive differential diagnosis." As a consequence, "...family physicians need to keep the diagnosis open in evaluating patients who present with pain in multiple joints." (page 1151, left hand column).

Many other examples are possible in which symptoms themselves provide inadequate information for determining their cause and appropriate treatment. Developmental delays may arise from a variety of underlying causes, including metabolic defects such as phenylketonuria, lead or mercury poisoning, epilepsy, or a variety of genetic defects. A diet low in phenylalanine helps patients with phenylketonuria (in which an enzyme deficiency prevents phenylalanine metabolism), but is useless in other conditions involving developmental delay or seizures. Lead and mercury poisoning can perhaps helped by administration of chelating agents which are useless in diseases not caused by heavy metals. Antiepileptic drugs like valproate or lamictal can help developmental delays secondary to disruptions in brain function caused by seizures, but may be detrimental in disorders not caused by seizures.

The relationship between the molecular anomaly, 5'nucleotidase excess, and symptoms in the children described by Page et al. is not clear. As the authors point out, the disorder is not associated with actual uridine nucleotide deficits (and the symptoms do not match those of the only known pyrimidine deficit disorder, Orotic Aciduria). Uridine and related pyrimidine compounds were initially tested in these patients because the first one identified presented with megaloblastic anemia (a primary symptom of orotic aciduria), which was later attributed to her anti-seizure medication. The finding that uridine was helpful was actually fortuitous and does provide a basis for

asserting that uridine would be helpful in similar symptoms or symptom complexes associated with other diseases.

In addition, the cited Page et al paper is not the first publication of the use of uridine to treat 5'-nucleotidase excess. This was published earlier in Page, et al., "A Syndrome of Megaloblastic Anemia, Immunodeficiency, and Excessive Nucleotide Degradation," in Purine and Pyrimidine Metabolism in Man VII, Part B, Harkness, et al. eds (1991) pp. 345-348. The fact that between 1991 and the subject invention no one used uridine compounds to treat pathophysiological consequences of mitochondrial respiratory chain dysfunction is further evidence of its nonobviousness.

Prior to the effective filing date of the subject application, a number of diseases were known to be mitochondrial in origin. Yet they were not treated with pyrimidine nucleotide precursors. This observation refutes the Office's position that it would have been obvious to treat any and all mitochondrial diseases using pyrimidine nucleotide precursors. As evidence, applicants submit copies herewith of the following eight journal articles:

DiMauro, et al, "Mitochondrial encephalomyopathies: where next?", Revista de Neurologia (1999) 28(2):164-168.

Luft, "Review: The development of mitochondrial medicine", Proc. Natl. Acad. Sci. USA (September 1994) 91: 8731-8738.

Beal, "Mitochondrial dysfunction in neurodegenerative diseases", Biochimica et Biophysica Acta (1998) 1366: 211-223.

Blass, "Brain metabolism and brain disease: is metabolic deficiency the proximate cause of Alzheimer dementia", J. Neurosc. Res. (2001) 66: 851-856.

Bowling, et al., "Minireview: Bioenergetic and Oxidative stress in neurodegenerative diseases", Life Sciences (1995) 56(14): 1151-1171.

Beal, "Mitochondria, free radicals, and neurodegeneration", Current Opinion Neurobiol. (1996) 6: 661-666.

Browne, et al, "Oxidative damage and mitochondrial dysfunction in neurodegenerative diseases", Biochem. Soc. Trans. (1994) 22: 1002-1006.

Schulz, et al., "Mitochondrial dysfunction in movement disorders", Current Opinion in Neurology (1994) 7:333-339.

In view of the above, it is clear that a *prima facie* case of obviousness has not been generated in this case. Withdrawal of the obviousness rejection is respectfully requested.

Favorable action on this application is awaited.

Respectfully submitted,

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